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EXAMINER

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UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte TIECHENG A. QIAO, JEFFREY W. LEON,
and KURT M. SCHROEDER

Appeal 2009-0894
Application 10/625,424
Technology Center 1700

Decided:¹ May 1, 2009

Before DEMETRA J. MILLS, ERIC GRIMES, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a
microarray. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

¹ The two-month time period for filing an appeal or commencing a
civil action, as recited in 37 C.F.R. § 1.304, begins to run from the
decided date shown on this page of the decision. The time period
does not run from the Mail Date (paper delivery) or Notification
Date (electronic delivery).

Statement of the Case

Background

The Specification teaches “a microarray comprising a support with a layer of microspheres immobilized in a 2-dimensional plane, in a randomly or orderly distributed pattern” (Spec. 6, ll. 10-12). According to the Specification, “[e]ach microsphere in the microarray has a distinct optical signature that can distinguish that microsphere from other microspheres that have different optical signatures--that is, the signature is unique” (Spec. 6, ll. 7-9).

The Claims

Claims 1-17 are on appeal. We will focus on claims 1 and 13 which are representative and read as follows:

1. A microarray comprising:
a support; on which is disposed;
a layer of microspheres bearing biological probes;
wherein said microspheres comprise at least one colorless
and non-fluorescent latent colorant that can be developed to
a colored state and used to identify said microsphere.
13. The microarray of claim 1 wherein the microspheres
are immobilized on a two dimensional support by a gelation
process.

The prior art

The Examiner relies on the following prior art references to show unpatentability:

Litt	US 4,092,408	May 30, 1978
Wang	US 4,663,277	May 5, 1987
Chee et al.	US 6,429,027 B1	Aug. 6, 2002
Leblans et al	US 2004/0069857 A1	Apr. 15, 2004

The issues

A. The Examiner rejected claims 1-5, 7-12, and 14-17 under 35 U.S.C. § 103(a) as being obvious over Chee and Leblans (Ans. 3-4).

B. The Examiner rejected claim 13 under 35 U.S.C. § 103(a) as being obvious over Chee, Leblans, and Wang (Ans. 4-5).

C. The Examiner rejected claims 1, 3, 5, and 6 under 35 U.S.C. § 103(a) as being obvious over Chee and Litt (Ans. 5-6).

A. 35 U.S.C. § 103(a) over Chee and Leblans

The Examiner rejected claims 1-5, 7-12, and 14-17 under 35 U.S.C. § 103(a) as being obvious over Chee and Leblans (Ans. 3-4).

The Examiner finds that “[t]he microspheres disclosed by Chee et al. differ from the claimed invention in that the reference does not disclose that the dye is a colorless dye that can be developed to a colored state” (Ans. 4).

The Examiner finds that “Leblans et al. disclose photochromic dyes for identifying microspheres (see [0056]). The disclosed photochromic dyes are colorless and undergo an irreversible change in light absorption in the presence of specific wavelengths of electromagnetic radiation” (Ans. 4).

The Examiner finds that “[i]t would have been obvious to one of ordinary skill in the art to use the photochromic dyes disclosed by Leblans et al. to identify the microspheres disclosed by Chee et al. since the photochromic dyes disclosed by Leblans et al. undergo permanent color change” (Ans. 4).

Appellants contend that “Leblans et al. also fails to disclose a colorless, latent, non-fluorescent colorant as presently claimed. Leblans et al. discloses the use of fluorescent materials throughout the reference.” (App. Br. 4). Appellants also contend that “Leblans et al. fails to teach or suggest

any advantages in the use of colorless and non-fluorescent colorants as claimed by the instant invention. In fact, the reference teaches that the use of fluorescent compounds are suitable” (App. Br. 5). Appellants also contend that “surprising result of the present invention is that the colorless coding offers no detectable background fluorescence from microspheres, therefore detection is dramatically improved. As such, the dynamic range for measuring target analytes is greatly increased over the prior art” (App. Br. 5).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Did the Examiner err in finding it obvious to use colorless, nonfluorescent, photochromic dyes disclosed by Leblans for microcarriers in the microspheres of Chee?

Findings of Fact (FF)

1. Chee teaches a support, specifically “a first substrate with a surface comprising a plurality of assay locations, each assay location comprising a plurality of discrete sites” (Chee, col. 3, ll. 50-52).
2. Chee teaches that the “substrate further comprises a population of microspheres comprising at least a first and a second subpopulation, wherein each subpopulation comprises a bioactive agent. The microspheres are distributed on each of the assay locations” (Chee, col. 3, ll. 52-56).
3. Chee teaches that the “beads are generally put onto the substrate randomly, and thus several different methodologies can be used to ‘decode’ the arrays” (Chee, col. 5, ll. 1-3).

4. Chee teaches that “unique optical signatures are incorporated into the beads, generally fluorescent dyes, that could be used to identify the chemical functionality on any particular bead” (Chee, col. 5, ll. 4-6).

5. The Specification teaches that “[i]n another preferred embodiment, [a] photo initiation process is used as a physical means to switch latent colorants into detectable optical signatures. Several examples include[] . . . photo initiated photochromic dye formation” (Spec. 18, ll. 10-16).

6. Claim 9 teaches a “microarray of claim 1 wherein the material with a latent color is . . . a photochromic dye” (Claim 9).

7. Leblans teaches “a ‘microcarrier’ also termed ‘microsphere’ . . . relates to a reaction volume or a support which may be made from, for example, any materials that are routinely employed in high-throughput screening technology and diagnostics” (Leblans 3 ¶ 0039).

8. Leblans teaches “reading or writing of a code on a microcarrier” (Leblans 2 ¶ 0012).

9. Leblans teaches that the “code may also be written by photochroming. Photochromic materials of interest undergo an irreversible change in light absorption that is induced by electromagnetic radiation, most common applications involve irreversible changes in color or transparency on exposure to visible or ultraviolet light” (Leblans 6 ¶ 0056).

10. Leblans teaches that “[m]ost of the interesting compounds are thermally irreversible, i.e. they do not change back to the original colorless state at room temperature. Advantageous photochromic dyes are those that cannot be bleached back to their original state” (Leblans 6 ¶ 0056).

11. Leblans teaches that “[p]hotochroming is potentially faster and easier to control than the bleaching of fluorescent dye, because the coloration is normally linear with incident power” (Leblans 6 ¶ 0056).

12. Leblans teaches that “[r]eadout is simplified because it is sufficient to take an image that reveals the code on a transparent background. A pattern written by localized bleaching in a fluorescent bead, on the other hand, would require a confocal microscope to detect it” (Leblans 6 ¶ 0056).

13. Leblans teaches that “[w]hen encoding by photochroming, we obtain a completely transparent microcarrier in which a colored pattern is written. This is much easier to detect and there is therefore no need for a confocal microscope, a standard light microscope is sufficient” (Leblans 13 ¶ 0152).

Principles of Law

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). The Supreme Court has recently emphasized that “the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 416. “If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.” *Id.* at 417.

Moreover, an “[e]xpress suggestion to substitute one equivalent for another need not be present to render such substitution obvious.” *In re Fout*, 675 F.2d 297, 301 (CCPA 1982). As noted by the Court in *KSR*, “[a] person of ordinary skill is also a person of ordinary creativity, not an automaton.” 550 U.S. at 421.

Analysis

Chee teaches a microarray comprising a support and a layer of microspheres bearing biological probes, where the microspheres comprise a colorant (FF 1-4). Leblans teaches microspheres which comprise a photochromic colorant, which is colorless and nonfluorescent, and which can be developed to a colored state and used to identify the microsphere (FF 7-13).

Applying the *KSR* standard of obviousness to the findings of fact, use of the photochromic colorant in microspheres as taught by Leblans as the optical signature in the microspheres of Chee represents a combination of known predictable elements. Such a combination is merely a “predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 417.

Furthermore, Leblans provides specific reasons to utilize the photochromic colorants in the place of the fluorescent labels taught by Chee, since Leblans teaches that “[p]hotochroming is potentially faster and easier

to control than the bleaching of fluorescent dye, because the coloration is normally linear with incident power” (Leblans 6 ¶ 0056; FF 11). Leblans also teaches that “[r]eadout is simplified because it is sufficient to take an image that reveals the code on a transparent background. A pattern written by localized bleaching in a fluorescent bead, on the other hand, would require a confocal microscope to detect it” (Leblans 6 ¶ 0056; FF 12).

Consequently, the ordinary artisan would have reasonably substituted the photochromic colorants of Leblans for the fluorescent dyes of Chee in order to use faster, easier dyes, linear with incident power which can be read with less expensive equipment in a simpler manner (FF 11-13).

We are not persuaded by Appellants’ argument that “Leblans et al. also fails to disclose a colorless, latent, non-fluorescent colorant as presently claimed. Leblans et al. discloses the use of fluorescent materials throughout the reference.” (App. Br. 4). This is simply not correct. Leblans expressly teaches, and appears to prefer, photochromic colorants for the microspheres (FF 11-13). Appellants’ Specification clearly identifies photochromic colorants as colorless, latent, non-fluorescent colorants (FF 5). Appellants’ claim 9 even claims photochromic colorants as within the scope of the invention (FF 6). Thus, Leblans clearly teaches that the photochromic colorants can form “a completely transparent microcarrier in which a colored pattern is written” (Leblans 13 ¶ 0152; FF 13).

We are not persuaded by Appellants argument that “Leblans et al. fails to teach or suggest any advantages in the use of colorless and non-fluorescent colorants as claimed by the instant invention. In fact, the reference teaches that the use of fluorescent compounds are suitable” (App.

Br. 5). Leblans expressly teaches that photochromic colorants are superior, noting that “[p]hotochroming is potentially faster and easier to control than the bleaching of fluorescent dye, because the coloration is normally linear with incident power” (Leblans 6 ¶ 0056; FF 11).

Even if Leblans preferred fluorescent dyes, Leblans teaches the use of photochromic colorants (FF 11-13). “All the disclosures in a reference must be evaluated, including nonpreferred embodiments, and a reference is not limited to the disclosure of specific working examples.” *In re Mills*, 470 F.2d 649, 651 (CCPA 1972) (citation omitted). In this case, Leblans is reasonably understood as actually preferring the photochromic colorants, particularly since Leblans discusses several advantages of photochromic over fluorescent compounds (FF 11-13).

Appellants contend that a “surprising result of the present invention is that the colorless coding offers no detectable background fluorescence from microspheres, therefore detection is dramatically improved. As such, the dynamic range for measuring target analytes is greatly increased over the prior art” (App. Br. 5). However, Appellants provide no evidence to support any unexpected results. This is argument without evidence. “[A]rguments of counsel cannot take the place of evidence lacking in the record.” *Estee Lauder Inc. v. L'Oreal, S.A.*, 129 F.3d 588, 595 (Fed. Cir. 1997) quoting *Knorr v. Pearson*, 671 F.2d 1368, 1373 (CCPA 1982). *See also In re Baxter-Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) (“[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.”).

Conclusion of Law

The Examiner did not err in finding it obvious to use colorless, nonfluorescent, photochromic dyes disclosed by Leblans for microcarriers in the microspheres of Chee.

B. 35 U.S.C. § 103(a) over Chee, Leblans, and Wang

The Examiner rejected claim 13 under 35 U.S.C. § 103(a) as being obvious over Chee, Leblans, and Wang (Ans. 4-5).

The Examiner finds that “[n]either Chee et al. nor Leblans et al. disclose the immobilization of the microspheres by a gelation process” (Ans. 4). The Examiner finds that “Wang discloses an immunoassay for a virus accomplished by utilizing microspheres coated with antiviral antibodies. The reference discloses that the method of the immunoassay involves immobilizing the microspheres by placing the microspheres in a gel” (Ans. 4-5).

Appellants contend that “[a]s no reference suggests the use of a color-free, non-fluorescing material that can be switched on to form a colored material, the references fail to provide any suggestion to produce the presently claimed invention” (App. Br. 7). Appellants also contend that “[t]he Examiner fails to provide any motivation for using a non-fluorescing, colorless molecule that can be developed to form a colored material. The references fail to disclose a colorless and non-fluorescent latent colorant as claimed by the instant invention” (App. Br. 8).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Did the Examiner err in finding it obvious to use photochromic dyes disclosed by Leblans for microcarriers in the microspheres of Chee and the gel based microsphere assay of Wang?

Findings of Fact

14. Wang teaches that the “microspheres are placed in a gel” (Wang, col. 9, l. 48).

Analysis

As discussed *supra*, Leblans specifically teaches the use of photochromic dyes in microspheres (FF 7-13) and Chee teaches detection of biological analytes using microspheres on supports (FF 1-4).

The Examiner reasonably finds that Wang teaches immobilization of microspheres in gel (FF 14).

We are not persuaded by Appellants’ argument that “no reference suggests the use of a color-free, non-fluorescing material that can be switched on to form a colored material, the references fail to provide any suggestion to produce the presently claimed invention” (App. Br. 7). As discussed *supra*, Leblans specifically teaches the use of such a photochromic material, noting that “[p]hotochroming is potentially faster and easier to control than the bleaching of fluorescent dye, because the coloration is normally linear with incident power” (Leblans 6 ¶ 0056; FF 11). Leblans also teaches that the photochromic colorants can form “a completely transparent microcarrier in which a colored pattern is written” (Leblans 13 ¶ 0152; FF 13).

We are also not persuaded by Appellants’ argument that “[t]he Examiner fails to provide any motivation for using a non-fluorescing,

colorless molecule that can be developed to form a colored material” (App. Br. 8). Leblans provides specific reasons to utilize the photochromic colorants in the place of the fluorescent labels taught by Chee, since Leblans teaches that “[p]hotochroming is potentially faster and easier to control than the bleaching of fluorescent dye, because the coloration is normally linear with incident power” (Leblans 6 ¶ 0056; FF 11). Leblans also teaches that “[r]eadout is simplified because it is sufficient to take an image that reveals the code on a transparent background. A pattern written by localized bleaching in a fluorescent bead, on the other hand, would require a confocal microscope to detect it” (Leblans 6 ¶ 0056; FF 12).

Conclusion of Law

The Examiner did not err in finding it obvious to use photochromic dyes disclosed by Leblans for microcarriers in the microspheres of Chee and the gel based microsphere assay of Wang.

C. 35 U.S.C. § 103(a) over Chee and Litt

The Examiner rejected claims 1, 3, 5, and 6 under 35 U.S.C. § 103(a) as being obvious over Chee and Litt (Ans. 5-6).

The Examiner finds that “Chee et al. disclose a two-dimensional array of microspheres randomly immobilized in wells of a substrate” (Ans. 5). The Examiner finds that “Litt discloses an enzyme label that interacts with colorless o-nitrophenol dyed sugar to produce a measurable color intensity” (Ans. 5). The Examiner finds that it would have been obvious “to provide the microspheres disclosed by Chee et al. with the dye label disclosed by Litt since the label disclosed by Litt allows the quantification of enzyme activity

directly from the intensity of the color produced by the enzyme reaction”

(Ans. 6).

Appellants contend that “[n]either reference alone or in combination teaches or suggests a colorless and non-fluorescent latent colorant as claimed by the instant invention” (App. Br. 10). Appellants contend that Litt is nonanalogous art since “Litt discloses an enzyme cauterized [sic, catalyzed] reaction that is incapable of producing a variety of colors” (App. Br. 10). Appellants contend that “[t]he instant invention claims a microarray with a layer of microspheres. Each microsphere is independently capable of changing color” (App. Br. 10).

Appellants also contend that the “combination of Chee et al. with Litt is inoperable . . . Utilizing the microspheres disclosed by Chee et al. and the dye disclosed by Litt, it becomes impossible to identify individual microspheres” (App. Br. 11).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Did the Examiner err in finding it obvious to use enzyme labels disclosed by Litt for microcarriers in the microspheres of Chee?

Findings of Fact

15. Litt teaches that

With a fluorescent label, measurement of bound or unbound labelled antigen is achieved by any convention[al] fluorescent spectrometer. With an enzyme label, measurement of labelled antigen is achieved by measuring enzyme activity. This is conventionally done colormetrically by contact with a colorless o-nitrophenol dyed sugar and measuring the change in color intensity caused by cleavage

of the sugar from the dye by reaction of the sugar with the enzyme label to thereby release the dye.

(Litt, col. 7, ll. 46-55.)

16. Chee teaches that the microspheres may be labeled and that labels include enzymes (Chee, col. 19, ll. 28-36).

17. Chee teaches that “a single code can be assigned to multiple agents if the agents are functionally equivalent” (Chee, col. 22, ll. 60-61).

Analysis

Chee teaches a microarray comprising a support and a layer of microspheres bearing biological probes, where the microspheres comprise a colorant (FF 1-4). Litt teaches the use of colorless enzymatic labels which form color upon contact with their substrate (FF 15).

Applying the *KSR* standard of obviousness to the findings of fact, we conclude that use of the enzymatic labels as taught by Litt as the optical signature in the microspheres of Chee represents a combination of known predictable elements. Such a combination is merely a “predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 417.

We are not persuaded by Appellants’ argument that “[n]either reference alone or in combination teaches or suggests a colorless and non-fluorescent latent colorant as claimed by the instant invention” (App. Br. 10). Litt specifically teaches a colorless latent colorant, the o-nitrophenol dyed sugar, which becomes colored upon contact with the enzyme (FF 15). Appellants have provided no evidence that Litt’s o-nitrophenol dyed sugar is not non-fluorescent.

We are not persuaded by Appellants' argument that Litt is nonanalogous art since "Litt discloses an enzyme cauterized [sic, catalyzed] reaction that is incapable of producing a variety of colors" (App. Br. 10). We are also not persuaded by Appellants' contention that "[t]he instant invention claims a microarray with a layer of microspheres. Each microsphere is independently capable of changing color" (App. Br. 10).

Claim 1 does not require that the microspheres produce a variety of colors nor does claim 1 require that each microsphere is independently capable of changing color (*see* Claim 1). Claim 1 simply requires microspheres which bear biological probes and comprise a colorless and non-fluorescent latent colorant. Litt teaches a colorless and non-fluorescent latent colorant which an ordinary practitioner with ordinary creativity would reasonably have combined with the microspheres of Chee, particularly since Chee teaches that "labels include enzymes" (Chee, col. 19, l. 36).

We are also not persuaded by Appellants' argument that the "combination of Chee et al. with Litt is inoperable . . . Utilizing the microspheres disclosed by Chee et al. and the dye disclosed by Litt, it becomes impossible to identify individual microspheres" (App. Br. 11). Claim 1 does not require the ability to identify individual microspheres (*see* Claim 1). Further, Chee teaches that enzymes can function as labels (FF 16) and Chee also teaches that a single code can be used (FF 17). Here, we decline to read a limitation to "identify individual microspheres" into the claims. "[L]imitations are not to be read into the claims from the specification." *In re Van Geuns*, 988 F.2d 1181, 1184 (Fed. Cir. 1993) (citing *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989)).

Conclusion of Law

The Examiner did not err in finding it obvious to use enzyme labels disclosed by Litt for microcarriers in the microspheres of Chee.

SUMMARY

In summary, we affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Chee and Leblans. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 2-5, 7-12, and 14-17 as these claims were not argued separately.

We affirm the rejection of claim 13 under 35 U.S.C. § 103(a) as obvious over Chee, Leblans, and Wang.

We affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over Chee and Litt. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 3, 5, and 6 as these claims were not argued separately.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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